



Review Article

A neurologist's approach to delirium: Diagnosis and management of toxic metabolic encephalopathies



Vaishnav Krishnan ^{*}, Lester Y. Leung, Louis R. Caplan

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, United States

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ABSTRACT

Toxic metabolic encephalopathies (TMEs) present as an acute derangement in consciousness, cognition and behavior, and can be brought about by various triggers, including endocrine and metabolic disturbances, exogenous toxins, pain and infection. Also referred to as “delirium” or “acute confusional states,” TMEs are characterized by 1) an altered level of consciousness and activity, 2) global changes in cognition with inattention, 3) a fluctuating course with disturbances in the sleep-wake cycle, and 4) asterixis and myoclonus. The pathophysiology of this syndrome is poorly understood. Imbalanced neurotransmitter signaling and pathologically heightened brain inflammatory cytokine signaling have been proposed as candidate mechanisms. Focal brain lesions can also occasionally mimic TMEs. A neurological examination is required to identify the presence of focal findings, which when present, identify a new focal lesion or the recrudescence of prior ischemic, inflammatory or neoplastic insults. Diagnostic testing must include a search for metabolic and infectious derangements. Offending medications should be withdrawn. Magnetic resonance imaging, cerebrospinal fluid analysis and electroencephalography should be considered in select clinical situations. In addition to being an unpleasant experience for the patient and family, this condition is associated with extended hospital stays, increased mortality and high costs. In individuals with diminished cognitive reserve, episodes of TME lead to an accelerated decline in cognitive functioning. Starting with an illustrative case, this paper provides a neurologist's approach to the diagnosis, differential diagnosis and management of toxic metabolic encephalopathies.

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1. Introduction

Toxic metabolic encephalopathies (TMEs), variously known as “acute confusional states,” “sepsis-associated encephalopathy,” “delirium,” or “intensive care unit (ICU) psychosis” represent a serious and common neuropsychiatric syndrome associated with morbidity, prolonged hospitalization and financial costs, as well as increased psychological distress to the patient and family [1–3]. TMEs are canonical demonstrations of how distributed central nervous system circuits responsible for arousal, perception and focus are susceptible to systemic infectious, toxic or metabolic derangements. The brain's reaction to such derangements is often relatively acute, and a variety of different irritants often produce the same nonspecific behavioral reactions [4]. Nevertheless, perhaps due to heterogeneities in symptomatology and presentation, this condition remains under-recognized [5], and it has spurred the generation of several psychometric tools to assist with the rapid diagnosis of this condition [6]. TMEs often lead to persistent neurocognitive alterations even after offending triggers have been addressed effectively [7]. While serving on the neurology consult service in a multispecialty tertiary referral center, we obtained numerous consultations for “altered mental status.” The specific questions ranged from concerns about nonconvulsive status or

ischemic stroke to worries about the presence of undiagnosed dementia. In this clinical review designed for internists, we provide a neurologist's approach to the diagnosis and differential diagnosis of acute confusional states.

2. Case

A 91 year-old woman with systolic congestive heart failure presented to the cardiology clinic. At baseline, she is physically and cognitively independent. She was volume overloaded by examination, and so was electively admitted for diuresis. Over the next 48 h, high dose intravenous furosemide was administered with an appropriate treatment response. However, her serum creatinine increased from 1.0 to 1.8 mg/dL (estimated creatine clearance [CrCl] of 17 mL/min), and her systolic blood pressures reduced from the 130–140 mm range to 90–100 mm. She was transferred to the cardiac care unit (CCU) for milrinone therapy, which improved her renal function and blood pressures. However, on the second day of her CCU stay, she was noted to be confused, paranoid, and tremulous with intermittent jerking movements in all four extremities. When mobilized by physical therapy staff, she was unable to ambulate independently, and her knees appeared to intermittently give way. A noncontrast computed tomography scan of her head identified mild cerebral atrophy without hemorrhage, and a comprehensive laboratory investigation showed only an

^{*} Corresponding author. Tel.: +1 617 667 4700.

E-mail address: vkrishn@bidmc.harvard.edu (V. Krishnan).

elevated creatinine (1.3, CrCl 22 mL/min). Neurology was consulted for “altered mental status with jerking movements.” On exam, the patient was awake, alert and oriented only to her name. She was easily distracted and could not recall the months of the year backwards. She followed commands and did not display paraphasias. Cranial nerve examination was normal, and extremity movements were contaminated by intermittent myoclonic jerks that would affect one extremity at a time. The strength of individual muscle groups was normal, but she displayed an inconsistent and involuntary increase in tone. She had prominent bilateral asterixis. She was diagnosed with a toxic metabolic encephalopathy and no further diagnostic testing or neuroimaging was undertaken. Over the next several days, her mental status gradually improved as her cardiac and renal parameters returned to baseline. On the day of discharge five days later, her family noted that her responses were still delayed, but she was oriented and much less distractible.

3. Pathophysiology

Unraveling the basic biology of metabolic encephalopathy and delirious states remains the subject of active translational investigation. Hypoxia, hypoperfusion, infection, medications, alcohol withdrawal, and other triggers all appear to give rise to similar neurophysiological changes leading to global cognitive dysfunction of TMEs. Age and pre-existing dementia are major risk factors for the development of delirious states, suggesting that diminished “cognitive reserve” remains a key vulnerability factor [8]. For simplification, we identify three main pathophysiological themes that deserve significant attention.

First, two main neurotransmitter systems have been implicated in the clinical manifestations of acute confusional states. Reduced central acetylcholinergic signaling can directly result in cognitive impairment: this is exemplified by the iatrogenic development of delirium in vulnerable individuals following the administration of medications with prominent anticholinergic activity. These include first generation antihistamines (e.g., diphenhydramine, meclizine), tricyclic antidepressants (e.g., imipramine, amitriptyline) and antispasmodic agents for overactive bladder (e.g., tolterodine, oxybutynin). A rat model of low dose atropine administration recapitulates the neurocognitive impairments, electroencephalographic slowing and sleep impairments of typical anticholinergic encephalopathic states [7,9], but has not yet been implemented more extensively to identify specific cholinergically innervated brain regions that are responsible for behavioral impairments in metabolic encephalopathies [10]. The success of antidopaminergic agents in addressing the hyperactivity and agitation of delirium have led some to propose that excess dopaminergic signaling also plays a role. In support of this theory is the observation that excess dopamine supplementation in patients with Parkinson's disease can result in delirium. Overall, both of these neurotransmitter systems are best thought of as modulators rather than primary mediators of inattention and disorientation.

Second, serum levels of a variety of proinflammatory cytokines (e.g., interleukin-8 and tumor necrosis factor alpha) and anti-inflammatory cytokines (e.g., interleukin-10) appear to be elevated in patients with acute confusional states [7]. Recent work has identified specific panels of cytokines that seem to distinguish encephalopathy in “inflamed” (i.e., those with infection or sepsis) versus “noninflamed” patients [11]. Cytokines are thought to act on neurons through humoral routes (by directly activating macrophages in regions that lack a functional blood brain barrier, such as the circumventricular organ) or through the activation of cytokine receptors on vagal afferent neurons [12,13]. Pro-inflammatory cytokines may act directly on endothelium to result in impaired cerebrovascular autoregulation in sepsis [14]. Cytokines do cross the blood brain barrier, but with the advent of more sensitive and quantitative cytokine assays, we are just beginning to collect data on how cerebrospinal fluid cytokine levels may predict the occurrence of delirium [15,16]. Preliminary experiments using a model of polymicrobial sepsis in mice have shown that

persistent brain elevations TNF- α (tumor necrosis factor- α) and IL-6 (interleukin-6) may be responsible for long-term neuropsychological sequelae following bacterial infections [17].

Encephalopathy associated with kidney or liver failure is likely related to an accumulation of unexcreted medications or toxic physiological metabolites (many of which have not yet been identified). Hepatic encephalopathy has traditionally been conceptualized as a direct consequence of elevated ammonia levels [18], which itself is sufficient to enhance glycolysis and depress mitochondrial function [19]. Patients with minimal hepatic encephalopathy (MHE, cirrhotic patients who have subtle impairments in cognitive function only detected with neuropsychological testing) have been the subjects of functional magnetic resonance imaging studies. MHE patients demonstrated altered functional connectivity in a number of “resting state networks” [20]. Resting state networks are interconnected cortical and subcortical brain regions that are activated when a subject is awake and at rest and demonstrate abnormal connectivity in a number of neurodegenerative conditions including early Alzheimer's disease. In contrast to ammonia, the encephalopathy associated with renal failure (“uremic encephalopathy” or “dialysis dementia”) may be related to the accumulation of “guanidino” compounds (including guanidinosuccinic acid and methylguanidine) [21]. Associated electrolyte and acid-base derangements may also contribute, though less significantly [18].

For a given patient, one or many of these factors may be contributory. A pre-morbid dementia resulting in diminished cognitive reserve [22], sensory deprivation (e.g., lack of hearing aids), together with environmental triggers that result in pain and involuntary immobilization (e.g., use of restraints, urinary catheters), may all combine with the above medical and iatrogenic etiologies to raise the risk and prolong the course of metabolic encephalopathy [1].

4. Clinical manifestations and approach to physical examination

A relatively acute onset of new behavioral symptoms with a fluctuating course remains the key distinguishing feature between dementia and toxic metabolic encephalopathies; hence, neurologists prefer the term “acute confusional state.” The American Psychiatric Association formally identifies delirium as having i) core features of rapid and abrupt onset of impaired attention and altered sensorium, together with ii) changes in “at least one cognitive domain” (e.g., recent memory and orientation.) and iii) “associated features” (e.g., changes in sleep wake cycle, worsening in the evening) [23].

Rather than describing patients as “altered,” it is preferable to report specific alterations in i) activity (ranging from hypoactive abulia to agitated delirium), ii) *arousal* (ranging from alertness to stupor), and iii) *cognition*, which occurs within specific domains (attention, memory, language, etc.) [24]. Perceptual disturbances such as audiovisual hallucinations and delusions may be prominent features. Subtle difficulties with focus and attention are often the first sign of an ensuing encephalopathy, and are characterized by delayed reaction time and easy distractibility. Global inattention typically contaminates other abnormalities on mental status testing, such as difficulties with calculation, short-term recall and incorrect responses to simple orientation questions.

Inattentiveness is typically followed by diminished arousal or changes in the level of activity (ranging from severe agitation and hyperactivity to *abulia*, a hypoactive state with diminished spontaneity). There have been efforts to distinguish between “hypoactive” and “hyperactive” delirious states. From studies of patients with focal lesions, *abulia* has been linked to dysfunction within circuits connecting the frontal lobes to basal ganglia structures, including the caudate and accumbens nuclei, thalamus and midbrain [25]. In contrast, focal lesions in hyperactive patients typically disturb posterior circuits connecting occipitoparietal cortices to limbic structures within the mesial temporal lobe [26]. In patients without focal lesions, this distinction simply reflects a spectral response to the same underlying neurological insult

[22]. The classical example of a hyperactive delirium without a focal lesion is *delirium tremens*, a syndrome of confusion, agitation, autonomic hyperactivity, tremors and seizures which occurs in the setting of alcohol withdrawal [27].

Motor manifestations of metabolic encephalopathy tend to create significant confusion among non-neurologists. Asterixis, a sudden loss of postural tone, when occurring bilaterally, is a characteristic sign of metabolic encephalopathies and is not specific to hepatic dysfunction. Myoclonus, a brief twitch of a muscle or group of muscles, is another commonly observed sign. When this affects the lower extremity muscles, it results in gait difficulties and postural instability. Together, asterixis and multifocal myoclonus are often described as “shaking” or “jerking” and are reported as “seizures” or “tremor.” Finally, one can also observe *paratonia* or *gegenhalten*, a type of hypertonia where patients display an inconsistent and involuntary increase in resistance to passive extremity movements. Paratonia may also result in gait difficulties.

When a toxic metabolic encephalopathy is strongly suspected, we recommend clarifying the history from caregivers about the patient’s baseline cognitive abilities and the time course over which the change in behavior occurred. Home and hospital medication lists require close review to identify benzodiazepines, opiate narcotics or anticholinergics. Given that paranoia and terrifying hallucinations can often be a prominent component of metabolic encephalopathies, one needs to approach the patient gently and in a manner that would promote trust and collaboration. Rather than jumping directly to questions related to orientation to place and date, we suggest first evaluating for the presence of difficulty with simple attentional tasks (such as recalling the months of the year backwards, or a digit span test). Then, focus should be shifted to demonstrating the presence or lack of signs of focal cortical dysfunction. Difficulties with language suggest focal dysfunction in the dominant frontal or temporal lobes and associated structures. These may manifest as subtle *paraphasic* errors (such as “truck” instead of “duck”), agrammatic or fragmented speech, or difficulties with fluency and comprehension. Reading and writing can also be tested to assess these language functions. Visual field testing is essential since this may be the only elementary sign of a focal temporal and parietal lobe lesion. When possible, one needs to closely observe for the presence of hemi-inattentiveness or *hemineglect*, which indicates a contralateral cerebral hemisphere lesion.

Stuporous patients may have negligible participation in formal mental status testing. Attention must then be shifted to testing cranial nerve function and a sensorimotor examination to exclude focality or structural explanations for their stupor [28]. Focal deficits may reflect a post-ictal phenomenon. A general physical examination is essential to identify meningismus and a source of possible infection or pain.

5. Focal/structural lesions

A number of focal lesions can mimic the clinical features of toxic and metabolic encephalopathies with very subtle localizing signs. Rather than providing a comprehensive catalog, we list some common scenarios here and refer our readers to associated references:

- In patients with cardiovascular risk factors, the acute onset of altered attentional processing, particularly when associated with extremes in blood pressure, should raise suspicion for ischemic stroke or intraparenchymal hemorrhage involving the non-dominant parietal or temporal lobes [26,29,30]. A subtle hemiparesis with ipsilateral neglect may be the only clue.
- In patients at risk for cardioembolism, a shower of small emboli may lead to a diffuse derangement in processing speed without resulting in obvious focal signs. This extends to patients with atrial fibrillation who are not on anticoagulation, valvular heart disease, or following catheterization or surgical manipulation of the left heart and aorta.

- Cerebral venous sinus thrombosis may occasionally result in bilateral thalamic edema from venous congestion or infarction that can result in an acute confusional state, stupor or coma [31,32]. A search for venous thrombosis must be undertaken when the patient has comorbid conditions associated with systemic hypercoagulability, such as malignancy, sepsis, etc.
- The presence of confusion associated with vivid visual, tactile and auditory hallucinations may suggest damage in the distribution of bilateral posterior cerebral arteries [33]. Similarly, a form of hypertensive encephalopathy known as posterior reversible leukoencephalopathy syndrome (PRLS or PRES) can result in transient vasogenic edema in occipitoparietal white matter and can result in confusion accompanied by cortical blindness or seizures [34]. PRES is often observed in patients who are immunosuppressed on calcineurin inhibitors including tacrolimus.
- Encephalopathy may be caused by acute or chronic subdural hemorrhages, particularly in patients with known significant brain atrophy, in alcoholics, and in patients who are maintained on anticoagulants such as warfarin. Subdural hemorrhages along the vertex or at the anterior poles of the temporal lobes can irritate underlying cortex and produce subtle seizures, manifesting as a classical fluctuating encephalopathy [28].
- The meningoencephalitis associated with the herpes simplex virus (HSV) results in preferential damage to the mesial temporal lobes and the medial orbitofrontal cortex, leading to language dysfunction, seizures, short term memory loss, and an abulic encephalopathy [35].

6. Diagnostics, ancillary testing and the role of neurology consultation

A comprehensive metabolic and infectious investigation is likely to identify an offending etiology in the vast majority of cases of TME. Testing should include electrolyte panels, a complete blood count with differential, liver function tests, a urinalysis, a plain chest film, as well as blood and urine cultures. Checking serum ammonia levels, arterial blood gases and the examination of cerebrospinal fluid may be utilized selectively. In parallel, one must review the patient’s medication list to identify and discontinue or avoid medications with known anticholinergic activity, as well as opiate narcotics, corticosteroids, sedatives and other medications with sedative activity (e.g., cyclobenzaprine and gabapentin). In patients with dementia, sensory deprivation and immobility (i.e. through wrist restraints and urinary catheterization) may be the sole precipitant of an acute confusional state without metabolic or infectious derangements, and therefore these interventions need to be minimized.

When feasible, we recommend obtaining a noncontrast CT (computed tomography) scan of the head. In addition to identifying hemorrhages (including acute and chronic subdural hemorrhages), today’s CT scans can augment a clinical assessment of overall brain health. One may find focal atrophy, or bilateral periventricular white matter hypoattenuation (signifying chronic microvascular ischemic changes), both of which may suggest a predisposition to the development of delirium. CT imaging may also show prior small infarctions as circumscribed hypodensities or larger infarctions as lobar encephalomalacia, and these findings may explain the recurrent development of focal neurological signs in conjunction with an acute confusional state (“recrudescence”). To definitively diagnose acute ischemic stroke or to exclude new neoplastic lesions or conditions such as PRES, an MRI (magnetic resonance imaging) is essential. Gadolinium contrast may be considered when neoplasia and focal infections or abscesses are highest on the differential. MR or CT venography is a must when central venous sinus thrombosis is suspected.

Continuous video-electroencephalography (cvEEG) remains the gold standard to diagnose nonconvulsive seizures or nonconvulsive status epilepticus (NCSE), the clinical manifestations of which can range from a “twilight state” with intermittently delayed responsiveness to coma [36]. EEG in the vast majority of TME cases will typically show varied degrees of etiologically nonspecific diffuse slowing in the theta

(3–7 Hz) or delta range (1–3 Hz), and may also have a few epileptiform discharges or triphasic waves (a type of discharge canonically observed in liver failure) [37]. These “abnormalities” should not be treated indiscriminately with anticonvulsant agents. The absence of epileptiform discharges in the first 4 h of recording generally denotes that nonconvulsive seizures are unlikely to be the explanation for persistent confusion [38]. To avoid the unnecessary and excessive use of EEG, we recommend that the cvEEG be strongly considered only in the following clinical scenarios:

- Those with a known history of epilepsy or who have had a clinical convulsion in the course of their confusional state.
- Patients younger than 18 [39].
- Patients with a history of acute or old brain injury (including trauma, prior stroke or anoxia). Fresh blood products of acute intracranial hemorrhages (including subarachnoid, intraventricular and subdural hemorrhages) are especially prone to trigger seizures [40].
- Patients exposed to medications known to lower seizure threshold (bupropion, tramadol, fluoroquinolones and metronidazole, among others).
- Comatose or stuporous individuals with subtle ocular movement abnormalities (e.g., nystagmus, bobbing) or unexplained, transient, abrupt alterations in blood pressure or heart rate [41].

Overall, we recommend prompt neurologic consultation for those patients suspected of TME when 1) a comprehensive laboratory and pharmacologic evaluation has not identified any obvious culprit derangements, 2) patients have a history of drug-refractory epilepsy or structural brain disease with or without focal or lateralizing features on their examination, and 3) MR imaging or continuous long term video EEG is being strongly considered.

7. Management and prognosis

Foremost emphasis must be placed on elucidating the underlying cause(s), and therapies should be targeted at remediating all identified insults. In patients with poor cognitive reserve, very subtle derangements may be sufficient to trigger a TME (e.g., a slight hyponatremia). Frequent doses of benzodiazepine therapy in conjunction with fluid and thiamine supplementation remain the mainstay of therapy in the management of the autonomic hyperactivity and seizures associated with alcohol withdrawal [27]. Aside from alcohol withdrawal, when convulsive seizures occur in the setting of a metabolic encephalopathy, one may initiate anticonvulsant therapy at nonsedating doses to lower the risk of seizures and avoid frequent benzodiazepine injections. First- and second-generation antipsychotics, procholinergic agents and benzodiazepines have been utilized to “treat” the confusion, agitation and disorientation of acute confusional states. The use of antipsychotics for delirium altogether remains controversial: their strong sedative effects, which may be beneficial in agitation, can themselves perpetuate an encephalopathy. The risk of extrapyramidal symptoms (acute dystonia, tremor and rigidity) and QTc prolongation necessitates a “start low and go slow” approach when utilizing these agents. While first and second generation antipsychotics may not differ in efficacy, the side effects of first generation agents including haloperidol require more frequent monitoring [42,43]. For this reason, we urge avoidance of haloperidol and other first generation antipsychotics, particularly with repeated use in high doses. A number of delirium prevention trials using “prophylactic” antipsychotic agents have not shown significant efficacy [42,44]. Prophylactic cholinesterase inhibition such as rivastigmine may in fact lead to increased mortality [45]. As our knowledge of the basic neurobiological mechanisms of encephalopathic states continues to grow, we will continue to require large-scale randomized pharmacologic treatment and prevention trials to better answer this question.

The design of delirium prevention strategies has received more attention lately, as it can be argued that many cases of delirium may be predictable [7]. A number of cost-effective multi-component delirium-

prevention protocols have been successfully implemented [46–48]. These programs typically involve combinations of: early assessment of bowel and bladder function, aggressive mobilization, intravenous hydration and close monitoring of electrolytes, medication review and avoidance of polypharmacy, frequent pain assessments, structures to enhance the quality of sleep, and pathways to improve deficits in vision and hearing [2]. Much more emphasis needs to be placed on formalizing and developing protocols for nonpharmacological methods such as the Hospital Elder Life Program [47,49].

It has long been observed that demented patients who develop acute confusional states remain somewhat more impaired following the resolution of the acute illness, and seem to display a “new baseline.” Among patients with clinically diagnosed Alzheimer disease (AD), the occurrence of delirium during a hospitalization tends to accelerate AD-related cognitive decline by approximately 50% [50,51]. Even among patients without dementia, the occurrence of delirium following cardiac valve replacement surgery or coronary artery bypass grafting resulted in a significantly lower likelihood of patients returning to their preoperative level of functioning [52]. As mentioned above, the field has a limited understanding of the pathophysiological basis for such a phenomenon and will likely have to develop new neuroimaging and bioinformatic tools to further clarify such mechanisms.

8. Conclusions and future directions of research

Episodes of delirium or acute confusion represent a serious consequence of an underlying metabolic, infectious or inflammatory insult. These are associated with prolonged hospitalization, heightened mortality and increased financial costs. Age, pre-existing dementia, multiple medical comorbidities and polypharmacy are important risk factors. As our population's burden of dementia continues to grow in the absence of specific disease-modifying therapies, developing effective means to prevent delirium-induced cognitive decline will be essential. First and foremost, we need to promote a greater awareness of this condition within all communities of health care providers. We must improve our methods of identifying at-risk patients through the use of serological, cerebrospinal fluid and genetic analysis, and implement routine nonpharmacological techniques to prevent and address delirium [7]. Only with a deeper understanding of the underlying molecular mechanisms can we begin to devise rationally designed medical treatments to prevent and treat delirium [49]. Finally, higher quality clinical studies are required to clarify the importance of i) phenomenologic distinctions within delirium subtypes (hypoactive versus hyperactive), ii) the value of prophylactic pharmacological therapy, and iii) potential therapies to reverse persistent cognitive alterations.

Learning points

- Toxic metabolic encephalopathies (TMEs), also known as “delirium” or “acute confusional states” represent an acute diffuse derangement in cognitive functioning and can be brought about by a variety of triggers, including infection, metabolic disturbances, pain and dehydration.
- The clinical hallmarks of TME include inattentiveness and a fluctuating course, and may be associated with symmetric motor manifestations such as asterixis, myoclonus and paratonia.
- A comprehensive metabolic and infectious work up must be conducted in each patient with an acute confusional state. Focal findings on the neurological examination, including hemiparesis, hemianopia, cortical blindness or aphasia may suggest an underlying focal process such as ischemic stroke, venous sinus thrombosis or hypertensive encephalopathy. Alternatively, they may represent the recrudescence of old cerebral lesions. A noncontrast computed tomography scan should be obtained to rule out “acute lesions” (e.g., hemorrhages and abscesses) and can also augment one's clinical assessment of overall brain health.

- In some, even after the derangement has been reversed, the occurrence of this syndrome may lead to a persistent impairment in cognitive functioning, setting up a “new baseline”.
- We suggest prompt neurological consultation in confused patients with a history of structural brain disease and refractory epilepsy, so that we may guide the use of electroencephalography and neuroimaging techniques.
- In patients with prominent agitation, low dose benzodiazepines and second-generation antipsychotics should be judiciously employed only in situations where the safety of the patient and caregivers is at stake.

Conflicts of interests

The authors disclose no competing financial or other sources of conflict of interest.

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